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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,760	06/21/2006	Hans-Jorg Treichler	2006_0804A	8707

513 7590 10/31/2007

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,760	TREICHLER ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The abstract of the disclosure is objected to because the first page of the WIPO document (WO 2005/061527), which has an abstract, has also been used as the abstract sheet in the instant specification. This is not acceptable if the instant claims are determined to be allowable at a later stage. The Office requires the abstract to be typed on a separate sheet of paper even though applicants intend using the abstract on the WIPO document for the instant application. Hence, applicants are requested to kindly type the abstract appearing on the first page of the WIPO document (WO2005/061527) on a separate sheet and file the same. Correction is required. See MPEP § 608.01(b).

Drawings

The drawings are objected to because Figures 3-6 do not indicate what parameters are plotted in the X and Y axes. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet"

or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the treatment and diagnosis of cancer does not reasonably provide enablement for the diagnosis and treatment of infection by microorganisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of predictability in the art
(D) The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 20-21 are drawn to a method of diagnosis and treatment of infection by microorganisms comprising applying a cobalamin derivative according to instant claim 1 carrying a diagnostic and a therapeutic agent respectively. The claim recitation is seen to include any type of infection by any microorganism.

The state of the prior art

The examiner notes that the prior art of record (Morgan et al, WO 95/27723) drawn to cobalamin derivatives teaches the use of such derivatives for the treatment of cancer and is silent regarding the diagnosis and treatment of infections by microorganisms.

The level of predictability in the art

There are several different types of infections by microorganisms and each has a different etiology (see for example The Merck Manual 1992, pages 86-107) and different treatments. A single class of compound cannot predictably diagnose or treat all such infections.

The amount of direction provided by the inventor

The specification (page 6) just recites that the instant compounds are of high value in the treatment and diagnosis of infections by pathogenic microorganisms.

The existence of working examples

The working examples set forth in the instant specification are drawn to therapy studies of radiolabelled cyanocobalamin on syngeneic tumor in mice. Despite this limited example there is little enabling disclosure for the scope of the methods using the compounds/compositions as instantly claimed. One of ordinary skill in the art would not extrapolate this data to the diagnosis and treatment of all types of infections by microorganisms since diagnosis and treatment of

cancers is quite different from diagnosis and treatment of infections by microorganisms. The etiology of both is different.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the use of the said compounds compositions for the diagnosis and treatment of infections by microorganisms. One of ordinary skill in the art would have to carry out experiments on different types of infections using the compounds as instantly claimed to study the efficacy of the compounds in the said methods of diagnosis and treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low" in claim 1 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 27 is drawn to the method of parent claim 21 wherein the cobalamin is effective in cancer imaging. Parent claim 21 is drawn to a method of treatment of neoplastic disease. Claim

27 is examined as being drawn to the method of parent claim 21 wherein the cobalamin is effective in cancer treatment.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-9, 12-13, 19, 21 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Morgan et al (WO 95/27723; document AJ in IDS of 06/21/2006).

Morgan et al teach cobalamin derivatives (abstract; Figure 8), wherein the central cobalt atom is attached to a cyanide group (R^1 = CN), R^2 is GABA-peptide (GABA is gama amino butyric acid), the positions labeled b, c and e in the structure of Morgan all have an amide group, i.e., the amino nitrogen bears a hydrogen and the 5' carbon of the ribose ring (bottom of the structure) has an OH attached to it. This structure of Morgan is seen to meet the limitations of instant claim 7, wherein X is a monodentate ligand, R^d is different from hydrogen (in Morgan's structure it R_2 which is GABA-peptide), $R^b = R^c = R^e = R^R$ = hydrogen in instant formula (I) and R_2 in Morgan's structure being GABA-peptide is also seen to meet the limitations of instant claim 7, wherein R^d is a sterically demanding organic group with 4 to 20 carbons. This substitution also meets the limitation of instant claim 9 since the gama amino butyric acid-

peptide substituent is seen as a spacer chelators that can chelate though the carbonyl oxygen and the amino nitrogen. This teaching of Morgan is also seen to meet the limitations of instant claims 1-4 and 8. In the above structure the cobalamin carries a peptide, which is seen as a therapeutic agent. Hence the structure also meets the limitations of instant claim 5 for a cobalamin carrying a therapeutic agent. R^1 = CN in the structure of Morgan is same as X = CN in instant formula (I). Morgan also teaches a complex of cyanocobalamin and acridine, chloroquine, quinacridine dyes (page 54, example 11). These are dyes that have a contrast on uptake by cancer and tumor cells and thus serve as imaging agents. This teaching meets the limitation of instant claim 5 for a cobalamin derivative carrying a diagnostic agent. Hence this teaching meets the limitations of instant claims 12-13 wherein X is cyano. Morgan teaches pharmaceutical compositions of the cobalamin derivatives in combination with a pharmaceutical carrier or diluent (page 41, lines 29-34; limitation of claim 19). The cobalamin derivatives of Morgan are also useful in a method of treatment of neoplastic disorders (page 76, claims 77-78 of Morgan; meets limitations of instant claims 21 and 27).

The instant claims are drawn to cobalamin derivatives that have no binding affinity or low binding affinity to transcobalmin II and retaining activity as a vitamin B_{12} substitute. The art above is seen to meet these limitations. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-7, 10-12, 14-18, 20 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan et al (WO 95/27723; document AJ in IDS of 06/21/2006) as applied to claims 1-5, 7-9, 12-13, 19, 21 and 27 above, and further in view of Grissom et al (US 6,797,521) and Collins (US 5,739,313).

This rejection covers limitations not covered by the anticipation rejection above.

Morgan teaches cobalamin derivatives, pharmaceutical compositions and their use in a method of treating neoplastic diseases, as explained above. However, Morgan et al do not teach or exemplify a cobalamin derivative carrying a radioactive metal, but does suggest the use of radioisotopes conjugated the cobalamin (page 36, lines 20-24). In addition to the teaching above, Morgan also teaches different types of linkers (or spacers) that can be homobifunctional, heterobifunctional, trifunctional that can be used to couple other molecules. The linkers have typically 6 to 30 atoms in the chain and the atoms can be C, N, O or S. Diaminoalkyl and aminoalkyl carboxylic acids can also be used (page 14 through page 18). One of skill in the art will recognize from this teaching that such bifunctional groups in addition to acting as linkers/spacers can also chelate metal ions and hence act as spacer-chelators

Grissom, drawn to cobalamin, teaches dyes as diagnostic agents that are attached to cobalamins as diagnostic and prognostic markers to distinguish cancer cells from healthy cells (col. 2, line 1 through col. 10, line 17).

Collins, drawn to cobalamin, teaches the use of radionuclide labeled cobalamins that also have chelators/linkers attached to them (col. 3, line 5 through col. 6, line 51). Several radioisotopes are suggested for use including some of those recited in instant claims 11 and 14. A variety of homobifunctional and heterobifunctional linking reagents known in the art can be used as linkers (col. 4, lines 20-34). The cobalamins can have cyano, methyl adenosyl groups attached to the central cobalt atom (col. 3, line 65 through col. 4, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make cobalamin derivatives as instantly claimed and use them in a method of

treating and diagnosing neoplastic diseases since the use of such analogous derivatives for the same purpose is seen to be taught in the prior art.

One of skill in the art would be motivated to make the derivatives and use them in a method as instantly claimed inorder to look for potentially better derivatives that diagnose cancer cells and treat them without affecting healthy cells.

Conclusion

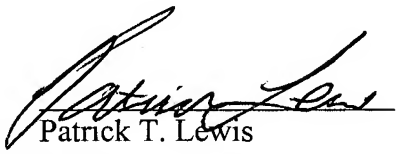
Claims 1-21 and 26-27 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK



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